Understanding causes of and developing effective interventions for schizophrenia and other psychoses

Jesus Perez,[1,2,3] Debra A Russo,[1,2,3] Jan Stochl,[1,2,3] Gillian F Shelley,[1] Carolyn M Crane,[1,2] Michelle Painter,[1] James B Kirkbride,[3,4] Tim J Croudace[5] and Peter B Jones[1,2,3*]

[1]CAMEO Early Intervention in Psychosis Service, Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK
[2]Department of Psychiatry, University of Cambridge, Cambridge, UK
[3]National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care, East of England, Cambridge, UK
[4]Division of Psychiatry, University College London, London, UK
[5]School of Nursing and Midwifery, University of Dundee, Dundee, UK

*Corresponding author

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Scientific summary

Causes of, and interventions for, psychoses

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Scientific summary

Background

Psychotic illnesses such as schizophrenia cause enormous disability and are expensive for sufferers and society. Developments in treatment interventions have been slow but mental health services have changed dramatically over the last decade.

A simple but radical idea concerns early-intervention services (EISs). In essence, EISs aim to identify people with psychosis promptly and treat them promptly. Anxiety, depression and short-lived individual psychotic features appear to put people at high risk (HR) of developing a full psychotic syndrome. Identifying and treating this HR phase in which people have an at-risk mental state for psychosis may improve outcomes.

Aims and intended outputs

We focused on people with first-episode psychosis (FEP) or mental states that put them at HR for FEP with the aim of identifying them early. One output was a method of educating general practitioners (GPs) and sixth-form colleges about psychosis and guiding their referral behaviour. We also aimed to investigate the nature and causes of the HR state and what leads to transition to FEP and to find a way of predicting the population prevalence of new cases to guide policy and service planning. There were several outputs of our programme:

- a web-deployed, evidence-based EIS planning tool for the NHS to predict the numbers of people requiring services by area
- knowledge of how best to detect HR for psychosis in primary care and schools
- a realistically complex understanding of person–place interactions in the genesis of HR and FEP.

The elements of our research programme are described below. We developed the Client Assessment Register (CAR), a user-friendly, computerised system that was used by clinicians and researchers within the team using local information technology systems and support. Our original intention was to use the information to develop an outcome assessment measure with considerable input from patients. Soon after we began the programme all NHS mental health trusts began to be encouraged to adopt the Health of the Nation Outcome Scales (HoNOS), later further developed for use as the ‘case mix’ adjustment for payment-by-results (PbR) funding of mental health services (HoNOS-PbR; treating people with more severe disorders and greater needs attracting greater funding from commissioners and vice versa). Understandably, our host NHS trust was keen to move wholesale to this measure, something that we supported even though it made some of our programme redundant.

Nevertheless, we significantly enhanced some aspects of the programme through an efficient use of available resources. For example, we systematically followed all individuals at HR for psychosis in the context of a separate study, the Prospective Analysis of At-risk mental states and Transitions into psycHosis (PAATH) study, with a naturalistic, observational design, not in our original application to the National Institute for Health Research (NIHR). This study was linked with several epidemiological and separately funded neurobiological research projects, representing an example of efficiencies in science and demonstrating the inter-relation between the different components of the programme.

Incidence of psychosis in socially and ethnically diverse settings

Much of our knowledge about the clinical epidemiology of psychotic disorders comes from studies based in predominantly urban settings, often cities, and predicated on outmoded health service models. These studies have indicated a rich landscape of variation in incidence according to standard epidemiological dimensions such as age, sex, social class and ethnicity, with further effects visible at the urban neighbourhood level including ethnic density. Far less is known about psychosis epidemiology and its public health impact across the gamut of population settlements, including mixed urban, suburban and rural populations.

Method

We estimated the administrative incidence of psychosis and its variation along sociodemographic dimensions using a case ascertainment system in a well-established EIS called CAMEO [see www.cameo.nhs.uk (accessed 18 January 2016)], with two linked teams serving a mixed urban–rural area. We built on our previous epidemiological studies, such as the East London First-Episode Psychosis (ELFEP) study and the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (ÆSOP) study. Also, by strategic alignment with other projects, such as the Social Epidemiology of Psychoses in East Anglia (SEPEA), we obtained useful data on the incidence of psychosis across eastern England.

Key findings

We estimated the overall incidence of FEP at 45.1 per 100,000 person-years [95% confidence interval (CI) 40.8 to 49.9 per 100,000 person-years]. Incidence rates varied across eastern England but were two to three times higher than those on which EIS specifications were predicated by the Department of Health. Our data suggest considerable psychosis morbidity in diverse, rural communities.

Development of a population-level prediction tool for the incidence of first-episode psychosis (PsyMaptic)

Using these rich epidemiological data we developed and validated a population-level prediction tool capable of accurately estimating the expected incidence of psychiatric disorder (PsyMaptic). Applied to FEP as proof of concept, we showed that it was possible to predict the expected incidence in a given population within the prediction intervals forecast by our models.

Key findings

A model with age, sex, ethnicity and population density performed most strongly, predicting 508 FEP participants in an EIS in East Anglia (95% CI 459 to 559 FEP participants), compared with 522 observed participants. The prediction tool for the incidence of psychotic disorders in England and Wales is freely available online [see www.psymaptic.org/ (accessed 18 January 2016)]. This is in use by NHS England to support new policies on EIS waiting time targets.

The Liaison with Education and General practiceS cluster randomised controlled trial: liaison with general practices to detect and refine referrals of people with at-risk mental states for psychosis

General practitioners are usually the first health professionals contacted by people with early signs of psychosis. It is unclear whether increasing the intensity of liaison between primary care and secondary care improves the clinical effectiveness and cost-effectiveness of detecting people with, or at HR of developing, a FEP. This is important given political commitments to facilitate early intervention and decrease waiting times in mental health. We developed and tested a theory-based intervention to improve detection and

referral of these mental states. In a parallel process we did the same in sixth-form colleges, as described in *Cluster randomised controlled trial with 16+ educational institutions to detect and refine referrals of people with at-risk mental states for psychosis*.

Developing the intervention in primary care

We used the theory of planned behaviour (TPB) to understand the factors that influence the identification of individuals at HR of developing psychosis in primary care. We then designed an intervention tailored to individual practices aiming to improve identification and referral of HR individuals and those with FEP.

Feasibility

We designed and assessed the psychometric properties of a questionnaire to determine and measure beliefs that influence GPs' identification of individuals at HR for psychosis in primary care. This work informed the subsequent design of the Liaison with Education and General practiceS (LEGS) educational intervention to help GPs detect these individuals.

Method

A semistructured discussion group elicited beliefs underlying GPs' motivations to detect these individuals and informed the construction of a preliminary 106-item questionnaire incorporating all constructs outlined in the TPB. A pilot phase involving 79 GPs from 38 practices across 12 counties outside the trial area defined the determinants of intention to identify HR individuals. Item response theory identified which items could be removed.

Key findings

The final instrument included 73 items and showed acceptable reliability ($\alpha = 0.77$–0.87) for all direct measures. Path analysis revealed that all of the TPB measures significantly predicted intention. Subjective norm, reflecting perceived professional influence, was the strongest predictor of intention. Collectively, the direct measures explained 35% of the variance of intention to identify individuals at HR, indicating a good fit with the TPB model. Information from the pilot questionnaire identified specific barriers and we designed strategies to change practice.

Cluster randomised controlled trial in primary care

Methods

The LEGS study was a cluster randomised controlled trial (cRCT) involving primary care practices (clusters) in the county of Cambridgeshire and Peterborough. Consenting practices were randomly allocated into two groups: (1) low-intensity liaison between primary care and secondary care, a postal campaign consisting of biannual guidelines to help in the identification and referral of individuals with early signs of psychosis and (2) the high-intensity intervention described in the previous section, which, in addition to the postal campaign, included a specialist mental health professional to liaise with each practice and support the theory-based educational package. Concealed randomisation involved a randomly permuted sequence in blocks, with 12 strata and 96 blocks. Practices that did not consent to be randomised constituted a practice-as-usual (PAU) group. The high- and low-intensity interventions were implemented over a period of 2 years for each practice during the study period April 2010 to October 2013.

The primary outcome was the number of HR referrals to the EIS per practice site predicated on an assumption that the intensive intervention would double them. New referrals were assessed clinically and stratified into those who met criteria for HR or FEP (together: psychosis true positives) and those who did not fulfil such criteria for psychosis (false positives). Referrals from PAU practices were also analysed.

An economic evaluation quantified the cost-effectiveness of the interventions and PAU, using decision-analytic modelling. Cost-effectiveness was expressed as the incremental cost per additional true positive identified.

Findings

Of the 104 eligible practices, 54 consented to be randomised. Twenty-eight practices were randomised to low-intensity liaison and 26 practices were randomised to the high-intensity liaison. Two high-intensity practices withdrew. High-intensity practices referred more HR [incidence rate ratio (IRR) 2.2, 95% CI 0.9 to 5.1; $p = 0.08$), FEP (IRR 1.9, 95% CI 1.05 to 3.4; $p = 0.04$) and true positive (IRR 2.0, 95% CI 1.1 to 3.6; $p = 0.02$) cases. High-intensity practices also referred more false positives (IRR 2.6, 95% CI 1.3 to 5.0; $p = 0.005$); most (68%) of these were referred on to appropriate services.

The total costs per true positive referral in high-intensity practices were lower than those in low-intensity or PAU practices; the high-intensity intervention was the most cost-effective strategy.

Interpretation

Increasing the resources aimed at managing the primary–secondary care interface provides clinical and economic value in this setting.

Cluster randomised controlled trial with 16+ educational institutions to detect and refine referrals of people with at-risk mental states for psychosis

As with GPs, teachers are in a good position to notice early signs of psychosis in their students but may not know enough about psychosis to recognise what they see or how to access appropriate help.

Development of the intervention

We designed an instrument to elicit teachers' commonly held beliefs about identifying students at HR according to the TPB. The study protocol employed in primary care was replicated in educational institutions for students aged 16+ years.

Key findings

The response rate to our teacher questionnaire was poor: only 75 (9.5%) returned questionnaires from the invited sample of 793 such that there will have been response bias. Perceived behavioural control was the strongest predictor of intention. Subjective norm did not predict intention. Collectively, the direct measures explained 37% of the variance of intention to identify HR for psychosis. Teachers believed that their peers or superiors might not approve of them identifying HR students. The greatest source of social pressure came from the senior management team within the school. Teachers' confidence and control over identification was low; they held a strong view that identifying HR symptoms in students was not part of a teacher's role. Our questionnaire proved to be reliable, with the analysis supporting the predictive power of the TPB with regard to intention. We have confirmed the feasibility, reliability and acceptability of a TPB-based questionnaire to identify teachers' beliefs and intentions concerning the identification of individuals at HR for psychosis.

Status of the cluster randomised controlled trial

The pilot work informed the subsequent design of an educational intervention to help teachers detect HR students, replicating the methodology of the educational intervention in primary care. The implementation of the 2-year educational intervention and the subsequent 12-month counting of referrals is complete; statistical analysis continues.

The Prospective Analysis of At-risk mental states and Transitions into psycHosis

The principal objective of the PAATH study was to identify the proportion of individuals at HR for psychosis who make the transition into a psychotic illness and to elucidate the common characteristics that can help identify this population. Secondary objectives included various epidemiological and clinical analyses that would (1) contribute to an enhanced delineation of people at HR who are more likely to develop a full psychotic illness and (2) allow comparisons between HR and healthy volunteers (HVs) regarding sociodemographic and clinical characteristics, substance use, trauma history, functioning and quality of life.

Method

This prospective, naturalistic study assessed all individuals at HR for psychosis living in Cambridgeshire and Peterborough and detected during the duration of the trial, including those identified by GPs and 16+ educational institutions in the LEGS cRCT. Sixty help-seeking HR individuals, aged 16–35 years, were recruited from the CAMEO EIS in Cambridgeshire. Individuals were stratified into those who met the criteria for HR or FEP (true positives) according to the Comprehensive Assessment of At-Risk Mental States (CAARMS) and those who did not (false positives). HR participants were followed up for 2 years, attending nine interviews (baseline and then every 3 months until the end of the study) at which they completed structured interviews and a battery of questionnaires on sociodemographic characteristics, diagnosis, psychiatric morbidity, trauma history, substance use and functioning. A random sample of 60 HVs matched for age (16–35 years), sex and geographical area underwent the same battery of questionnaires at baseline, 1 and 2 years.

Key findings

Transition rates from high risk to first-episode psychosis

Only 5% of our HR sample (3/60) made a full transition to a psychotic disorder based on structured clinical diagnosis (10% when CAARMS criteria were employed) over the 2-year follow-up period. This is an important message to young people with HR mental states and to services: the risk of transition from HR to FEP is low over 2 years.

Psychiatric morbidity, functioning and quality of life in people with high-risk mental states

High-risk individuals had a higher prevalence of moderate or severe depression, anxiety, obsessive–compulsive behaviours and suicidality than did HVs. HR individuals had poor global functioning and low quality of life that, combined with a significant risk of suicidality, justifies special attention from mental health services and appropriate care pathways. These findings, together with the low transition rates, suggest that clinical interventions in individuals at HR should aim at targeting a broader range of psychopathology, especially mood and anxiety symptoms, rather than just focusing on the treatment and/or prevention of psychosis.

Linked psychometric analyses in other population samples indicated that psychotic experiences measure the severe end of a common mental distress factor, consistent with these results.

Substance use

The prevalence of substance use was similar in HR individuals and HVs except for past polydrug use; this was higher for HR individuals. No HR individual or HV met the criteria for a current or lifetime *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition, text revision (DSM-IV TR) substance use disorder or dependence. The HR substance use profile of our sample was significantly different from that of HVs in the same geographical area, other HR samples and FEP patients in our region at the time of their referral to CAMEO. Their pattern of comparatively low use was unlikely to be a major trigger for transition to a frank psychotic disorder. The main difference between HR individuals and HVs was frequency of substance use. Current frequency of use was significantly higher in HR individuals than in HVs for alcohol and

cannabinoids. Higher frequency of substance use in HR individuals combined with a significantly younger age of first use could contribute to the development of psychotic-like experiences. Substance use represents a clinical domain that requires further emphasis and more detailed consideration.

History of psychological, physical or sexual trauma

High-risk participants experienced significantly more traumatic events than HVs, but equivalent distress. Occurrences of trauma and age at which trauma occurred were the most likely predictors of becoming HR, not the degree of distress reported as a result of the trauma. Bullying was not specifically assessed, which is a weakness of the study. To enable differentiation between dissociative responses to trauma and genuine prodromal psychotic presentations, trauma characteristics in HR individuals should routinely be thoroughly assessed; that said, these may be the same phenomena.

First-rank symptoms and premorbid adjustment

Almost half of the HR individuals in our sample had at least one Schneiderian first-rank symptom (FRS) traditionally thought of as particularly indicative of schizophrenia; 21.6% had more than one FRS. Auditory hallucinations and passivity experiences were the most frequent. Passivity experiences were the only FRS significantly associated with transition to FEP. During childhood HR individuals, especially those with FRSs, had poorer premorbid functioning and adjustment across educational, social and peer relationship domains than HVs. However, this did not predict transition 2 years later. FRSs might not predict merely psychosis but also various psychiatric disorders and/or long-term impairment because of abnormal developmental processes.

Ongoing analyses and future steps

This programme has resulted in a large collection of rich data. We are continuing to analyse clinical characteristics that may indicate possible transitions to FEP. Future publications will evaluate premorbid adjustment, personality and psychological variables related to self-perception and attachment. We outline in the report our collaborations with NIHR portfolio neurobiological projects investigating biological mechanisms underlying the HR state as an example of back translation.

Conclusion

This NIHR programme developed our understanding of the social epidemiology of psychosis and HR mental states. This has led to a population prediction tool for FEP in current use by commissioners in England. In terms of identification by GPs of FEP and HR mental states we have shown that the TPB can be used to change GP behaviour: the intervention doubled identification of HR individuals and FEP and was cost-effective; these results are also being used to influence national policy and practice. This programme resulted in primary and secondary mental health care working closely together.

We have added to the evidence that the HR or at-risk mental state has much in common with depression and anxiety; it is not necessarily a harbinger of psychotic disorder. We believe that this new understanding will help young people at HR receive appropriate services. We have made a demonstrable contribution to the international debate on clinical risk for psychotic disorders and the relationships between depression, anxiety and psychotic experiences in young people.

Trial registration

The primary LEGS trial is registered as ISRCTN70185866 and UKCRN ID 7036. The PAATH study is registered as UKCRN ID 7798.

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Editorial contact: nihredit@southampton.ac.uk

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